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Role of Plants and Endophytes in the Biosynthesis of Secondary Metabolites for Natural Product Cancer Research

The chemical and biological diversity of nature is immeasurable and provides an extraordinary resource for the discovery of anticancer drugs[1]. The World Health Organization estimates that over 65% of the world's population relies on traditional medicine for their primary health needs [2-3]. Taxol, vincristine, etoposide, topotecan and vinblastine are a few examples of plant-derived therapies currently in clinical use for treatment of various forms of human cancer [4]. One significant problem associated with natural product drug research is nature only produces a relatively small amount of these phytochemicals. It is estimated that 38,000 yew trees must be harvested to generate 25kg of Taxol to treat 12,000 patients. In the last decade, endophytic fungi isolated from plant tissues have been identified as producers of these valuable drugs [5,6,7,8]. It is therefore imperative that the relationship between the plants and endophytic fungi during the accumulation of these secondary metabolites is studied. Insights from such research may provide alternative methods of natural product drug discovery which could be reliable, economical and environmentally safe.

There are three schools of thought on the origins of secondary metabolism in plants[9]. There is the argument that both plants and endophytic microbes co-evolved with pathways to produce these natural products. Another thought is that an ancient horizontal gene transfer took place between plants and microbes. The third suggests that either plants or endophytic fungi produce these secondary metabolites and transfers them to the other symbiont. Biosynthetic pathway studies using radio-labeled precursor amino acids reveal that plants and endophytic fungi have similar but distinct metabolic pathways for production of secondary metabolites [10, 11, 12]. Evidence to support the independent production of Taxol by endophytic fungi is the isolation of the gene 10-deacetylbaccatin-III-10-O-acetyl transferase from the endophytic fungus *Clasdosporium cladosporiodes* MD2[13] isolated from *Taxus media* (yew species). This gene is involved in the biosynthetic pathway of Taxol and shares 99% identity with *T. x media* (plant) and 97% identity with *T. wallichiana var. marirei* (plant). These data lead to the hypothesis that **plants and endophytic fungus through mutualistic symbiosis produces similar secondary metabolites**.

Recently it was reported that plants other than yew species also have endophytic fungi associated with them that make Taxol. This suggests that plants and fungi are independently capable of producing these important secondary metabolites. The question is whether bioactive phytochemicals of plants are produced by the plant itself or as a consequence of a mutualistic relationship with beneficial organisms in their tissue. The fact that a combination of inducing factors from both plants and endophytic fungi increased the accumulation of secondary metabolites in plants and fungi respectively[14, 15, 16] suggest that the fungal endophyte may play important roles in the biosynthesis of secondary metabolites. Therefore the symbiotic association and effects of plants and endophytes on each other during the production of other important pharmacological bioactive natural products such as camptothecin, vinblastine, and podophyllotoxin need to be explored. This could provide the framework for future natural product production through genetic and metabolic engineering[17-18].

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